

A hopping mechanism for cargo transport by molecular motors in crowded microtubules.

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Abstract

Most models designed to study the bidirectional movement of cargos as they are driven by molecular motors rely on the idea that motors of different polarities can be coordinated by external agents if arranged into a motor-cargo complex to perform the necessary work [1]. Although these models have provided us with important insights into these phenomena, there are still many unanswered questions regarding the mechanisms through which the movement of the complex takes place on crowded microtubules. For example (i) how does cargo-binding affect motor motility? and in connection with that - (ii) how does the presence of other motors (and also other cargos) on the microtubule affect the motility of the motor-cargo complex? We discuss these questions from a different perspective. The movement of a cargo is conceived here as a *hopping process* resulting from the transference of cargo between neighboring motors. In the light of this, we examine the conditions under which cargo might display bidirectional movement even if directed by motors of a single polarity. The global properties of the model in the long-time regime are obtained by mapping the dynamics of the collection of interacting motors and cargos into an asymmetric simple exclusion process (ASEP) which can be resolved using the matrix *ansatz* introduced by Derrida [23].

keywords - intracellular transport by molecular motors; bidirectional movement of cargo, traffic jam on microtubules; ASEP models.

1 Introduction

Research interest in the origins of the long-range bidirectional movement of particles (organelles, vesicles, nutrients) driven by molecular motors is motivated by fundamental questions concerning the nature of interactions between motors and their cargos as transport processes take place. A current explanation for the phenomenon relies on the idea that motors of different polarities act coordinately on the same particle at different times. If, however, they act in parallel, the bidirectional movement would reflect dominance of one or another kind of motor achieved by a *tug-of-war* mechanism [1], [2], [3], [4], [5]. An important question that remains in this context concerns the mechanisms that would promote such coordination [6]. Alternatives to the coordination or *tug-of-war* models in the literature arise from the possibility of attributing the phenomenon to a dynamic role of the microtubules [7] or to a mechanical coupling between different motors [8].

A general difficulty encountered within any of these views is related to the presence of other particles (including other motors) on the microtubule at a given time that are not directly involved with the transfer process. These other particles are expected to impose restrictions on motility and performance of the motors that are directly interacting with cargo at that time [9]. Contrarily to these expectations, however, data from observations of beads driven by kinesins in steady-state conditions indicate that the number of long length runs of such beads increases significantly as the density of motors at the microtubule increases, although their velocities remain essentially unaltered within a wide range of motor concentrations [10], [11]. Thus, the reality of traffic jam in crowded microtubules still challenges the current view of long-range cargo transport that presupposes an effective and controllable movement of the motor(s) arranged into a motor-cargo complex. This, of course, requires a certain degree of stability of motor-cargo interactions and motor processivity.

Our intention here is to discuss these problems from a different perspective by bringing into this scenario the model introduced in [12] to examine cargo transport as a *hopping* process. According

to that, motors and cargos would not assemble into complexes to put transport into effect. On the contrary, each motor would function as an active overpass for cargo to step over to a neighboring motor. In this case, the long-range movement of cargo is envisaged as a sequence of these elementary (short-range) steps either forwards or backwards. In [12] we examined the conditions under which this may happen, accounting for the fact that motor motility is affected by the interactions with other motors and with cargos on the microtubule. There, we considered the presence of a collection of interacting motors, all of them presenting the same polarity (kinesins may be thought of as prototypes) and a single cargo. Here, we examine whether it is possible to explain in a similar context the origin of the observed bidirectional movement displayed by cargos.

The particular mechanism we propose to substantiate the hopping differs from that suggested in [12]. It keeps, however, the same general ideas of the original. As it will be explained below, we view the hopping of cargo between motors as an effect of thermal fluctuations undergone by motor tails. The flexibility of the tails may promote contact and, eventually, exchange of cargo between neighboring motors.

As in [12], the model dynamics is mapped into an asymmetric simple exclusion process (ASEP) [13], [14], [15] whose stationary properties are resolved explicitly in the limit of very large systems. Other ASEP models have already been considered in the literature to study the conditions for motor jamming in the absence of cargo [9], [16], [17]. Our model is conceived to account explicitly for changes in the dynamics of the motors that at a certain instant of time are interacting with cargos.

The model is reviewed here in order to include a second cargo in the system, still keeping the presence of motors of a single polarity. We believe that this approaches more realistic situations in which the simultaneous presence of many cargos and motors on the same microtubule must be the prevailing situation [7]. We show that under these conditions, a cargo may be able to execute long-range bidirectional movement as it moves over clusters of motors assembled either at its back end or at the back end of the cargo in front. One may recognize in this a possibility for explaining the origins of self-regulation in intracellular transport since it has been suggested in the last few years that signaling pathways involved in intracellular traffic regulation can be performed simply

by the presence of cargos at the microtubule [18]. We then speculate that the passage of cargos on microtubules does not get blocked by motor jamming. On the contrary, jamming operates as an allied process to promote long runs of cargos across motor clusters. In this case, the density of motors on the microtubule can be identified as an element of control in intracellular transport since it directly affects the conditions for jamming.

It is worth mentioning that the model developed here does not rule out other possibilities, such as the *tug-of-war* or competition models. What we suggest is that the presence of motors of different polarities may not be essential to explain the origin of the bidirectional movement.

The hopping mechanism is presented in Sec.2. The kinetic properties of the extended version are developed in Sec.3, considering the presence of two cargos. In Sec.4 we present our results. Additional remarks and conclusions are in Sec.5.

2 An alternative for cargo driving

The stochastic model in [12] formulated in a lattice describes the dynamics of motors and cargos accounting for (i) steric interactions among different particles moving on the same microtubule; (ii) the presence of motors of a single polarity; (iii) the fact that cargos do not move if not driven by motors.

The crucial point is in item (iii) because it requires a specific model for motor-cargo dynamics as transportation takes place. We offer here a slightly different view from that in [12] keeping however the reliance on the ability of motors to transfer cargo. One way by which this may be achieved is sketched in *Figure (1)*. The stepping of cargo would be accomplished as it is released from a motor to which it is attached at a certain instant of time and then get attached to another (neighboring) motor either at the left or at the right – see *Figure (1a)*. This process, like the one discussed in [12], relies strongly on the flexibility of the motor’s tail. The idea was inspired by experimental results suggesting a dynamic role of the kinesin’s coiled-coil segment in the process [19], [20] and also by data indicating that under load, kinesin motors display an oscillatory movement [21] [22]. Here, we think of these oscillations as signaling fluctuations in the position of motor’s tail, not necessarily

being correlated with displacement of its center of mass. If this is the case, such oscillations would promote contact between neighboring motors favoring cargo exchange.

Accordingly, long-range displacements of cargo would reflect a hopping process extended over many neighboring motors which may be accomplished if these motors get jammed into clusters for sufficient long periods of time. Notice that the whole mechanism does not require special stability of cargo-motor binding. On the contrary, the transfer of cargo by a motor would be ease by a loose attachment between them.

The model in [12] was resolved explicitly considering the presence of a single cargo in the system. The averages for the quantities of interest were determined in steady-state conditions. We showed there that the long-range displacements of the cargo would occur predominantly in the backwards direction, i.e. in opposition to the direction of the movement of the considered motors. We shall show here that the same dynamics may lead cargo to display bidirectional movement if the system contains at least one more cargo interfering with the movement of the motors.

To examine the properties of the system containing two cargos and an arbitrary number of motors, we map it into the same ASEP as in [12] whose dynamics can also reproduce the scheme in *Figure(1)*.

2.1 Movement of motors and cargos: the ASEP model with two cargos

We consider a one-dimensional lattice with M sites, representing the microtubule with periodic boundary conditions. This system contains N motors and a number K of other particles - the cargos - that interact with motors in order to move. Each site can be occupied by a motor or by a motor attached to a cargo (*see Fig.1(a)*), otherwise it is empty. The total number of sites that remain unoccupied is $G = M - N - K > 0$. Here, we analyze the long-time behavior of this system for $K = 2$ and determine the average cargo velocity as a function of the parameters. The results indicate conditions for cargos to perform a type of long-range movement that share the characteristics of the observed bidirectional movement.

The map of the dynamics shown in *Figure.1* into the considered ASEP is carried out as follows.

First, each site is identified by its position $j = 1, 2, \dots, N$ at the lattice. Then, to each of these sites is associated a variable σ_j that assumes integer values 0, 1 or 2 such that $\sigma_j = 0$ if the site j is empty, $\sigma_j = 1$ if it is occupied by a motor; or $\sigma_j = 2$ if it is occupied by a motor attached to a cargo. With these, a configuration C of the lattice is specified by the set $\{\sigma_1 \sigma_2 \dots \sigma_N\}$. The dynamics of the ASEP that reproduces the elementary steps in *Fig. 1* can now be defined. For this, consider that at each time interval dt a pair of consecutive sites, say j and $j + 1$ are selected at random. The occupancy of these two sites is then switched according to the following rules

- (a) $10 \rightarrow 01$ with rate k , probability kdt
- (b) $12 \rightarrow 21$ with rate w , probability wdt
- (c) $21 \rightarrow 12$ with rate p , probability pdt

(1)

where the pair $(j, j+1)$ is represented by the values of the corresponding site variables (σ_j, σ_{j+1}) . The parameters k, w and p are the assigned probabilities per unit time (rates) for occurrence of the processes indicated. Process (a) describes the possibility for a motor (kinesin) that carries no cargo to step forward to a neighboring empty site (*Figure 1b*). Processes (b) and (c) account for the switching of the cargo between two neighboring motors. This accounts either for backward (b) or for forward steps (c). Notice that the dynamics conserves the number of particles of type-1 as well as those of type-2.

In order to investigate the long-time dynamics of a cargo resulting from these elementary steps we use the *matrix ansatz* introduced by Derrida [23], [15]. The idea is to represent the probability $P_{N,M}(C)$ of a configuration C of the system with N sites and M particles of type-1 as a trace over a product of N non-commuting matrices, each specifying the corresponding site occupancy:

$$P_{N,M}(C) = \frac{1}{Z_{N,M}} \text{Tr} \prod_{i=1}^N (\delta_{\sigma_i,1} D + \delta_{\sigma_i,2} A + \delta_{\sigma_i,0} E) \quad (2)$$

where

$$Z_{N,M} = \sum_{\{\sigma_i\}} \text{Tr} \prod_{i=1}^N (\delta_{\sigma_i,1} D + \delta_{\sigma_i,2} A + \delta_{\sigma_i,0} E) \quad (3)$$

is the normalization. The sum runs over all configurations for which $\sum_i^N \delta_{\sigma_i,1} = M$ and $\sum_i^N \delta_{\sigma_i,2} = K = 2$. In this product, a site i is represented by a matrix D if it is occupied by a motor ($\sigma_i = 1$) or by a matrix A if occupied by a motor with a cargo ($\sigma_i = 2$); if the site is empty it is represented

by a matrix E ($\sigma_i = 0$). In order to calculate averages over these configurations in the stationary state, it is necessary at first to find the *algebra* that must be satisfied by these matrices such that the probabilities defined in (2) satisfy the stationary conditions [14],

$$\sum_{C'} P_{N,M}(C') \Gamma(C' \rightarrow C) - P_{N,M}(C) \Gamma(C \rightarrow C') = 0 \quad (4)$$

where the sum extends over all configurations of M motors distributed over $N - K$ lattice sites. Observe that the nonzero terms on the LHS of the above equation are those for which configurations C and C' differ from each other at most by the positions of a pair of consecutive sites, which can be reversed by any of the elementary processes defined by the dynamics in (1). In this case, each factor $\Gamma(C' \rightarrow C)$ (or $\Gamma(C \rightarrow C')$) must be replaced by the rate w , k or p for the corresponding elementary process that brings C back from C' (or C' from C).

The algebra corresponding to the ASEP defined by the dynamics (1) has been presented in ([12]) for $K = 1$:

$$\begin{aligned} DA - xAD &= E - D \\ DE &= E \\ EA &= E \\ EE &= E \end{aligned} \quad (5)$$

with

$$x = \frac{k + p}{w} \quad (6)$$

Here, we shall use this same algebra to evaluate the traces over products of matrices D , A and E that appear in calculating averages over the quantities that characterize the movement of a cargo. Before proceeding, however, a few remarks are in order.

2.2 Traffic profile in the system with two cargos

The model with two cargos is not ergodic. The dynamics preserves the number of empty spaces in each of the two partitions defined by the initial positions of the two cargos in the system with

periodic boundary conditions. In this case, all configurations C and C' that satisfy equation (4) must share the number of empty spaces in each of the partitions. Moreover, configurations in which the empty spaces are all concentrated in one of the two partitions must be excluded, for these do not satisfy (4) with the algebra (5).

We treat the initial conditions (*IC*), namely the number of empty spaces - h in one of the partitions and $G-h$ in the other, as *random variables*. This artifact shall account for the uncertainty one has in experimental data regarding the relative positions of the particles, and also for effects of random processes that are not explicitly described by the present model such as motor binding and unbinding at the microtubule. For computing averages, we shall account first for all possible configurations at fixed h and then average the results over h . The procedure is further specified observing that (a) because there is no reason to favor any initial configuration, we may consider that h is uniformly distributed and (b) in analogy with a situation of equilibrium, we take the average *annealing* as the averages over particle configurations are performed in parallel with average over h .

The measure $P_{N,M}(C_{(h)})$ of a configuration $C_{(h)}$ of a *subset-h* is written as the trace over a product of matrices A, D and E that satisfy the algebra in (5):

$$P_{N,M}(C_{(h)}) = \frac{1}{Z_{N,M}^{(h)}} \text{Tr}(D^{p_1} E^{k_1} D^{p_2} E^{k_2} \dots D^{p_k} E^{k_k} \mathbf{A} D^{p_{k+1}} E^{k_{k+1}} \dots D^{p_p} E^{k_p} \mathbf{A} D^{p_{p+1}} E^{k_{p+1}} \dots D^{p_{N-1}} E^{k_{N-1}} D^{p_N} E^{k_N}) \quad (7)$$

In the expression above, each p_i is a binary variable such that $p_i \in \{0, 1\}$, $i = 1, 2, \dots, N$ and $k_i = 1 - p_i$ satisfying

$$\begin{aligned} k_1 + k_2 + \dots + k_k + k_{p+1} + \dots + k_{N-1} + k_N &= h \\ \text{and} \\ k_{k+2} + k_{k+3} + \dots + k_p &= G - h \end{aligned} \quad (8)$$

The normalization

$$Z_{N,M}^{(h)} = W_{2-2}^{(h)} = W_{12-12}^{(h)} + W_{02-12}^{(h)} + W_{12-02}^{(h)} + W_{02-02}^{(h)} \quad (9)$$

is conveniently expressed in terms of the weights $W_{(\sigma_{i-1}\sigma_i\sigma_{i+1}\dots)(\sigma_{j-1}\sigma_j\sigma_{j+1}\dots)}^{(h)}$. These are defined as the sum over the traces corresponding to the configurations that belong to the subset h for which the occupation of the sites ... $i-1, i, i+1\dots$ and ... $j-1, j, j+1\dots$ in the n -tuples are fixed and specified by the values of the corresponding site variables $(\sigma_{i-1}, \sigma_i, \sigma_{i+1}, \dots)$ and $(\sigma_{j-1}, \sigma_j, \sigma_{j+1}, \dots)$, respectively.

The $P_{N,M}(C_{(h)})$ defined above must satisfy the stationary conditions

$$\sum_{C'_{(h)}} P_{N,M}(C'_{(h)}) \Gamma(C'_{(h)} \rightarrow C_{(h)}) - P_{N,M}(C_{(h)}) \Gamma(C_{(h)} \rightarrow C'_{(h)}) = 0 \quad (10)$$

where the sum extends over all configurations $C'_{(h)}$ that belong to the subset h . The transition rates $\Gamma(C'_{(h)} \rightarrow C_{(h)})$ lead configurations $C'_{(h)}$ into configurations $C_{(h)}$.

2.3 The average velocity of a cargo

Consistently with the above definitions we represent the average value $\langle v_{(h)} \rangle$ of the velocity of any of the two cargos at fixed h as

$$\langle v_{(h)} \rangle = \frac{1}{Z_{N,M}^{(h)}} \left\{ p W_{(21)-(2)}^{(h)} - w W_{(12)-(2)}^{(h)} \right\} \quad (11)$$

The configurations associated with $W_{(21)-(2)}^{(h)}$ are such that the specified cargo has one motor at its right side that allows it to move one step to the right at a rate p . Similarly, in the configurations associated to $W_{(12)-(2)}^{(h)}$ there is a motor at the left side of this cargo that allows it to move one step to the left at rate w . In both types of configurations the neighborhood of the other cargo is not specified.

It shall be convenient to subdivide the above sum into sums over configurations having the same trace. This is achieved by specifying in (11) the occupation of the sites that precede both cargos. For this, $\langle v_{(h)} \rangle$ is rewritten as

$$\begin{aligned} \langle v_{(h)} \rangle = & \frac{1}{Z_{N,M}^{(h)}} \left\{ p \left[W_{(121)-(12)}^{(h)} + W_{(121)-(02)}^{(h)} + W_{(021)-(12)}^{(h)} + W_{(021)-(02)}^{(h)} \right] \right. \\ & \left. - w \left[W_{(12)-(12)}^{(h)} + W_{(12)-(02)}^{(h)} \right] \right\} \end{aligned} \quad (12)$$

To proceed in the evaluation of (12) it is also convenient to replace the site variables $\{\sigma_i\}$ by block variables $\{m_i\}$ and $\{q_i\}$ $i = 1, 2 \dots k$, that assume integer values to represent, respectively, sequences of motors and empty sites in a configuration $C_{(h)}$. With these, the sum over configurations that contribute to $W_{(121)-(12)}^{(h)}$ for example, can be expressed as

$$\begin{aligned} W_{(121)-(12)}^{(h)} = \sum_{\{q_i\}}' \sum_{\{m_i\}}' & \text{tr}(D^{m_1} E^{q_1} D^{m_2} E^{q_2} \dots \\ & \dots D^{m_k} E^{q_k} D^{m_{k+1}} A D^{m_{k+2}} E^{q_{k+2}} \dots D^{m_p} E^{q_p} D^{m_{p+1}} A) \end{aligned} \quad (13)$$

with $m_{k+1}, m_{k+2}, m_{p+1} \geq 1$. Here, D^{m_i} (or E^{q_i}) indicates a product of m_i (or q_i) matrices D (or E). The symbol on the summation signals indicates that these are restricted to the configurations that satisfy the constraints in (8) for $0 < h < G$.

All the traces in the RHS of (12) can now be reduced with the aid of the algebra in (5). For this, we use the identity

$$D^K A E = x^K A E \quad (14)$$

that also follows directly from (5) [12]. The results are quoted as follows

$$\begin{aligned} W_{(12)-(12)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(ED^{m_i} AED^{m_k} ED^{m_j} AED^{m_{k+1}}) = \sum_{\text{conf}}' x^{m_i} x^{m_j} \text{tr}(E) \\ W_{(121)-(12)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(ED^{m_i} AD^{m_k} ED^{m_j} A) = \sum_{\text{conf}}' x^{m_i} x^{m_j} \text{tr}(E) \\ W_{(12)-(02)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(ED^{m_i} AED^{m_j} EA) = \sum_{\text{conf}}' x^{m_i} \text{tr}(E) \\ W_{(021)-(12)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(EAD^{m_i} ED^{m_j} A) = \sum_{\text{conf}}' x^{m_i} \text{tr}(E) \\ W_{(121)-(02)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(ED^{m_i} AD^{m_j} EA) = \sum_{\text{conf}}' x^{m_i} \text{tr}(E) \\ W_{(021)-(12)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(EAD^{m_i} ED^{m_j} A) = \sum_{\text{conf}}' x^{m_i} \text{tr}(E) \\ W_{(02)-(02)}^{(h)} &= \sum_{\text{conf}}' \text{tr}(EAEA) = \sum_{\text{conf}}' \text{tr}(E) \end{aligned} \quad (15)$$

The above expressions are independent of h . The only dependence on h in the evaluation of the weights comes from the multiplicity of the configurations. Configurations for which $h = 0$ or $h = G$ contribute with a factor $1/N$ with respect to the contributions from all other configurations that result in the same trace.

2.4 Average over the random variable

We now take the average of $\langle v_{(h)} \rangle$ over all realizations of h that assumes an integer value within the interval $h \in [1, G - 1]$ for $G > 2$, with equal probability. This is performed here as

$$\langle v \rangle = \frac{\sum_h \{pW_{(21)-(2)} - wW_{(12)-(2)}\}}{\sum_h Z_{N,\langle M \rangle}} \equiv \frac{\{p\bar{W}_{(21)-(2)} - w\bar{W}_{(12)-(2)}\}}{\bar{Z}_{N,\langle M \rangle}} \quad (16)$$

that corresponds to the average *annealing* in analogy to a situation of equilibrium. The averaged quantities are indicated by the bars over the corresponding symbols representing the weights \bar{W} and normalization \bar{Z} .

Now, observe that because the traces do not depend on h , then the sums in the above expression, both in the numerator and in the denominator, account for all possible configurations of arbitrary sequences of empty and occupied sites, keeping fixed just the *n-tuples* indicated in each term. With this, the restrictions imposed on the sums in (15) are removed.

2.5 Sum over configurations

We estimate the number of configurations that contribute to $W_{(\sigma_{i-1}\sigma_i\sigma_{i+1}\dots) - (\sigma_{j-1}\sigma_j\sigma_{j+1}\dots)}$ for a given *n-tuple* $(\sigma_{i-1}\sigma_i\sigma_{i+1}\dots) - (\sigma_{j-1}\sigma_j\sigma_{j+1}\dots)$ by fixing the relative position of the cargos ξ and counting for all possible sequences of 0's and 1's. We then sum over ξ observing the invariance of the trace under cyclic transformations. The results are compiled below.

$$\begin{aligned}
(a) \quad \overline{W}_{(12)-(12)} &\simeq \sum_{m_j=1}^{M-2} \sum_{m_i=1}^{M-m_j} \frac{(N-m_j-m_i-3)}{2} \binom{N-m_j-m_i-4}{M-m_j-m_i} x^{m_i} x^{m_j} \text{tr}(E) \\
(b) \quad \overline{W}_{(121)-(12)} &\simeq \sum_{m_j=1}^{M-2} \sum_{m_i=1}^{M-m_j} \frac{(N-m_j-m_i-3)}{2} \binom{N-m_j-m_i-5}{M-m_j-m_i} x^{m_i} x^{m_j} \text{tr}(E) \\
(c) \quad \overline{W}_{(12)-(02)} &\simeq \sum_{m_i=1}^M \binom{N-m_i-4}{M-m_i} [(N-m_i-3)x^{m_i}] \text{tr}(E) \\
(d) \quad \overline{W}_{(021)-(12)} &\simeq \sum_{m_i=1}^{M-2} \binom{N-m_i-5}{M-m_i-1} [(N-m_i-4)x^{m_i}] \text{tr}(E) \\
(e) \quad \overline{W}_{(121)-(02)} &\simeq \sum_{m_i=1}^{M-1} \binom{N-m_i-5}{M-m_i-1} [(N-m_i-4)x^{m_i}] \text{tr}(E) \\
(f) \quad \overline{W}_{(021)-(02)} &\simeq \binom{N-5}{M-1} [(N-4)] \text{tr}(E) \\
(g) \quad \overline{W}_{(02)-(02)} &\simeq \frac{1}{2} \binom{N-4}{M} \text{tr}(E)
\end{aligned} \tag{17}$$

Variables m_i and m_j indicate the number of possible consecutive motors at the left of the cargos in each of these configurations contributing to a given $W_{(\sigma_{i-1}\sigma_i\sigma_{i+1}\dots)-(\sigma_{j-1}\sigma_j\sigma_{j+1}\dots)}$. The sums over m_i and m_j are estimated here in the limit of very large systems for which $N \rightarrow \infty$ and $M \rightarrow \infty$ keeping the motor density $M/N \rightarrow \rho$ finite within the range $0 < \rho < 1$. In this limit, the sums converge to integrals and these integrals can be evaluated using Laplace's asymptotic method.

Consider, for instance, the sum (a) in (17). We use Stirling's formula $N! \sim \sqrt{2\pi N} N^N e^{-N}$ to approximate the factorials involving the variables N and M and define the new variables [24]

$$z \equiv m_i/N \quad \text{and} \quad y \equiv m_j/N. \tag{18}$$

z and y assume continuous values in this limit so that the referred sum converges to the integral

$$\overline{W}_{12-12} \sim \frac{N^3 (1-\rho)^4}{2\sqrt{2\pi N (1-\rho)}} e^{-N(1-\rho)\ln(1-\rho)} \int_0^\rho dy \int_0^{(\rho-y)} dz \sqrt{\frac{1-y-z}{\rho-y-z}} e^{Nh(y,z)} \frac{x^{Nz} x^{Ny}}{(1-y-z)^3}. \quad (19)$$

The function $h(y, z)$ in the expression above depends only on the sum $y + z$:

$$h(y, z) = h(y + z) = [1 - (y + z)] \ln[1 - (y + z)] - [\rho - (y + z)] \ln[\rho - (y + z)]. \quad (20)$$

Thus, by defining $\nu \equiv y + z$, (19) can be rewritten as

$$\sum_{\text{conf}} W_{12-12} \sim \frac{N^3 (1-\rho)^4}{2\sqrt{2\pi N (1-\rho)}} e^{-N(1-\rho)\ln(1-\rho)} \int_0^\rho dy \int_y^\rho d\nu \sqrt{\frac{1-\nu}{\rho-\nu}} \frac{e^{Nf_2}}{(1-\nu)^3} \quad (21)$$

where

$$f_2 = h(\nu) + \nu \ln x \quad (22)$$

In order to apply Laplace's method for estimating the above integral, it is convenient to change the order of the integration observing that

$$\int_0^\rho dy \int_y^\rho d\nu(\cdot) = \int_0^\rho d\nu \int_0^\nu dy(\cdot) \quad (23)$$

With this change, the integral in y becomes trivial and the double integral in (21) reduces to

$$I = \int_0^\rho \nu \sqrt{\frac{1-\nu}{\rho-\nu}} \frac{1}{(1-\nu)^3} e^{Nf_2(\nu)} d\nu \quad (24)$$

which can be estimated by its maximum at large N . For this, notice that $f_2(\nu)$ has a maximum at

$$\nu_{\max} = \frac{1-x\rho}{1-x}. \quad (25)$$

Thus, if

$$(A) \quad x\rho < 1 \quad (26)$$

the condition $\nu_{\max} < \rho$ can not be satisfied and the maximum contribution to the integral in (24) comes from the extremum of the interval at $\nu = 0$ which is a local maximum. The result is [25],

$$I_{f_2}^{A,C} \sim \left[(1-\rho) \frac{N}{2} \right] \frac{1}{N^2} \frac{1}{\sqrt{\rho}} \frac{\exp[-N\rho \ln \rho]}{[\ln(x\rho)]^2}. \quad (27)$$

If however,

$$(B) \quad x\rho > 1 \quad (28)$$

then ν_{\max} is localized inside the integration interval so that the integral in (24) is estimated as [25]

$$I_{f_2}^B \sim \left[(1 - \rho) \frac{N}{2} \right] \frac{(x - 1)^2}{(x)^{3/2}} \frac{1}{(1 - \rho)^{5/2}} \frac{(1 - x\rho)}{1 - x} \sqrt{\frac{2\pi}{N}} \exp \left\{ N \left[\ln x - (1 - \rho) \ln \frac{(x-1)}{(1-\rho)} \right] \right\}. \quad (29)$$

We use this same procedure to estimate all the remaining terms in expression (16). We merely quote the results below, making some extra comments when necessary.

For estimating the sum indicated as (b) in (17) we notice that the difference $\sum_{m_j, m_i} \Delta_{m_j, m_i}$ between the expression in the RHS of (b) and the sum in (a) is

$$\begin{aligned} \sum_{m_j, m_i} \Delta_{m_j, m_i} &\equiv \sum_{\text{conf}} W_{121-12} - \sum_{\text{conf}} W_{12-12} \\ &= -\frac{(N - M)^2}{2} \sum_{m_j=1}^{M-1} \sum_{m_i=1}^{M-m_j} \binom{N - m_j - m_i - 3}{M - m_j - m_i} \frac{x^{m_j} x^{m_i}}{N - m_j - m_i} \end{aligned} \quad (30)$$

Applying Laplace's method to the resulting integrals after taking the thermodynamic limit, it gives

$$\begin{aligned} \sum_{m_j, m_i} \Delta_{m_j, m_i} &\sim - \left[\frac{N^3 (1 - \rho)^5}{2 \sqrt{2\pi N (1 - \rho)}} e^{-N(1-\rho) \ln(1-\rho)} \right] \\ &\times \begin{cases} \frac{1}{N^2} \frac{1}{\sqrt{\rho}} \frac{\exp(-N\rho \ln \rho)}{(\ln x\rho)^2}, & x\rho < 1 \\ \text{or} \\ \frac{-\sqrt{\rho}}{(x)^{5/2}} (1 - x\rho) \frac{(1 - x)^2}{(1 - \rho)^{7/2}} \sqrt{\frac{2\pi}{N}} \exp \left\{ N \left[\ln x - (1 - \rho) \ln \frac{(x-1)}{(1-\rho)} \right] \right\}, & x\rho > 1 \end{cases} \end{aligned} \quad (31)$$

The sum over configurations that contribute to W_{12-02} in (17) - (c) is estimated through the asymptotic behavior of a single integral, which gives

$$\sum_{conf} W_{12-02} \sim \frac{N^2(1-\rho)^4}{\sqrt{2\pi N(1-\rho)}} e^{-N(1-\rho)\ln(1-\rho)} \quad (32)$$

$$\times \begin{cases} \frac{1}{N} \frac{1}{\sqrt{\rho}} \frac{\exp(-N\rho \ln \rho)}{|\ln x\rho|}, & x\rho < 1 \\ \text{or} \\ \frac{1}{(x)^{3/2}} \frac{(1-x)^2}{(1-\rho)^{5/2}} \exp \left\{ N \left[\ln x - (1-\rho) \ln \frac{(x-1)}{(1-\rho)} \right] \right\} \sqrt{\frac{2\pi}{N}}, & x\rho > 1 \end{cases}$$

Analogous procedures are used to estimate the sums over configurations of the kind W_{021-12} and W_{121-02} in (17) - (d) and (e), which coincide in this limit:

$$\sum_{conf} W_{021-12} \sim \sum_{conf} W_{121-02} \sim \frac{N^2(1-\rho)^4}{\sqrt{2\pi N(1-\rho)}} e^{-N(1-\rho)\ln(1-\rho)} \quad (33)$$

$$\times \begin{cases} \frac{1}{N} \sqrt{\rho} \frac{\exp(-N\rho \ln \rho)}{|\ln x\rho|}, & x\rho < 1 \\ \text{or} \\ \frac{1}{(x)^{5/2}} \frac{(1-x)^2}{(1-\rho)^{5/2}} \exp \left\{ N \left[\ln x - (1-\rho) \ln \frac{(x-1)}{(1-\rho)} \right] \right\} \sqrt{\frac{2\pi}{N}}, & x\rho > 1 \end{cases}$$

For the remaining sums indicated in (17) - (f) and (g), it is sufficient to estimate the relevant contributions to $O(\sqrt{N})$ which are

$$\sum_{conf} W_{02-02} \sim \frac{N}{2} \frac{(1-\rho)^4}{\sqrt{2\pi N(1-\rho)\rho}} e^{-N[(1-\rho)\ln(1-\rho)+\rho\ln\rho]} \quad (34)$$

and

$$\sum_{conf} W_{021-02} \sim N \frac{(1-\rho)^4 \rho}{\sqrt{2\pi N(1-\rho)\rho}} e^{-N[(1-\rho)\ln(1-\rho)+\rho\ln\rho]} \quad (35)$$

In the following, we analyze the results for the average velocity of a cargo obtained in this limit using the estimates above.

3 Results

The average velocity of a cargo in the system of interacting motors and cargos that obey the ASEP dynamics set in (1) can now be analyzed observing the differences in the expressions obtained above for the integrals in each of the asymptotic regions limited by the range of the product ρx of the two variables ρ and x . Such differences lead to distinct behaviors for $\langle v \rangle$ characterizing different phases of the system that, in turn, reflect the differences in the distribution of motors along the considered microtubule.

At a fixed value of x such that $x > 1$ and for

$$(a) \quad 0 < \rho \leq 1/x \quad (36)$$

$\langle v \rangle$ is obtained from the behavior of the integrals for $\rho x \leq 1$, resulting in

$$\langle v \rangle \sim \frac{(p - w) + |\ln \rho x| [2p\rho |\ln \rho x| + (2p\rho - w)] - p(1 - \rho)}{1 + 4 |\ln \rho x| + [\ln \rho x]^2} \quad (37)$$

Within the complementary region in which

$$(b) \quad 1/x \leq \rho \leq 1 \quad (38)$$

$\langle v \rangle$ is determined from the behavior of the integrals for $\rho x \geq 1$; we find

$$\langle v \rangle \sim -\frac{k}{x} \quad (39)$$

Notice that for any $x < 1$ the condition (a) $\rho x < 1$ is always satisfied so that the results for $\langle v \rangle$ are given in this case by (37) within the entire interval $0 < \rho < 1$. Thus, for small values of x the system does not exhibit phase transitions.

The behavior of $\langle v \rangle$ is shown in *Fig.2* for the whole range of motor density ρ , at fixed $k = 1$ and $w = 3$ and at various values of x (6).

We notice in these results that for varying ρ and for x slightly above 1, the average velocity of the cargo changes sign. This means that at steady state, which may be achieved at sufficiently

short times after an eventual change in motor density at the microtubule, cargos may adjust and change their direction of propagation moving across motor clusters.

4 Discussions and additional remarks

The mechanism for cargo transfer envisaged here is equivalent to a hopping process in which the associated rates depend on site occupation. Because motors move and their movement is affected by the presence of the cargos and all other motors on the microtubule, the long-time dynamics of the system must be examined globally.

Our results indicate that the existence of mutual interactions and the fact that many cargos are allowed to coexist at the microtubule are determinant for reproducing in this context the characteristics of the bidirectional movement. We show that within a certain range of motor density a cargo in this system executes long-range displacements in both directions. We may argue then that long-range cargo transfer is facilitated by traffic and specifically, by the assembly of motors into clusters, which characterizes traffic jam. The presence of the other cargos in the system is essential for this to occur as they function as additional obstacles that interfere in the motor density profile. Each cargo induces aggregation of motors at its back end. In turn, this provides the conditions for cargo to execute long-range displacements either backwards, over the aggregate assembled at its back end , as well as forwards, over the aggregate assembled at the back end of the cargo in front.

As it was originally formulated the model does not account for the possibility that a motor with one or more attached cargos may move as well. In fact, this is the only mechanism that is usually employed to describe cargo transport and it is the basis for *coordination* or *tug-of-war* models. Also, for simplicity we have considered interactions of a cargo with a single motor at a time. Should a set of motors be allowed to interact with the cargo to participate in the transfer process then the map into the ASEP would need to be modified accordingly. We are currently working on these possibilities by including into the dynamics (1) a process of the kind $20 \rightarrow 02$ that recovers ergodicity of the model [26]

We should emphasize that the occurrence of the long-range bidirectional movement as a consequence of the hopping processes devised here may happen by the action of motors of just one kind possessing a well defined polarity. Changes in motor density and related traffic profile suffice as a mechanism to control cargo direction and the size of the runs determined essentially by the extent

of motor clusters at jamming conditions. This offers a rather straightforward explanation for the data mentioned above suggesting that the number of long run-lengths performed by the observed beads increases significantly as the density of motors at the microtubule increases [11]. In addition, the results presented here indicate that, for sufficiently high values of the motor density for which $\rho > 1/x$, at the point where the model displays a phase transition, cargos would perform a uniform movement (on average) since their velocities become independent of ρ . Such behavior has also been observed in the same set of experiments.

As noticed by Ma and Chisholm [6], "little is known regarding motor traffic and how it correlates with the movement of cargo". Here, we offer a possibility based on the idea that the transport does not require the action of an external agent to coordinate the process, or a *tug-of-war* mechanism or even the existence of a mechanical coupling between two kinds of motors as proposed more recently [8]. Instead, it suggests that such coordination can be achieved by collective effects on the course of the dynamics as the system "self-organizes" so that it presents characteristics that reflect an internal (and global) order that does not have its origin in the characteristics of the external medium. It is then possible that the necessary transport in cells is accomplished just by adjusting the density of motors at the microtubule.

Accordingly, the presence of processive motors of different polarities that are normally required to explain the movement of a putative motor-cargo complex would not be necessary. Transportation here is based on a mechanism that requires formation of clusters of motors, not necessarily on their ability to travel along long distances.

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Figure Caption

Figure 1 - Dynamics of motors and cargos. (a) **Cargo transfer.** It happens here through a mechanism of hopping between neighbor motors. Due to the flexibility of the tail, the attached cargo may display small oscillations leading to the possibility of it being caught either by the motor at its left or by the motor at its right. The corresponding processes $12 \rightarrow 21$ or $21 \rightarrow 12$ are represented in the figure. (b) **The step of a motor.** The time spent by the motor with the two heads attached to the microtubule is much larger than the time it spends with just one of the heads attached [27], as a part of the "hand-over-hand" mechanism proposed to explain the kinetics of two-headed motor proteins [28]. Occupation of a site by a motor occurs here whenever it is occupied by the two heads of a motor. The motor step is then represented as $10 \rightarrow 01$ which is indicated in the figure.

Figure 2 - The average velocity of a cargo for $k = 1$ and $w = 3$ as a function of the density ρ of motors at the microtubule, for various values of parameter x .

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